



DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-945]

Schedules of Controlled Substances: Removal of Fenfluramine from Control

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration proposes to remove fenfluramine (chemical name: *N*-ethyl- α -methyl-3-(trifluoromethyl)phenethylamine), including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts is possible, from the schedules of the Controlled Substances Act (CSA). This scheduling action is pursuant to the CSA which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. Fenfluramine is currently a schedule IV controlled substance. This action would remove the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule IV controlled substances, on persons who handle (manufacture, distribute, reverse distribute, import, export, dispense, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle fenfluramine.

DATES: Comments must be submitted electronically or postmarked, on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Interested persons may file written comments on this proposal in

accordance with 21 CFR 1308.43(g). The electronic Federal Docket Management System will not accept comments after 11:59 PM Eastern Time on the last day of the comment period. To ensure proper handling of comments, please reference “Docket No. DEA-945” on all electronic and written correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration encourages commenters to submit all comments electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the webpage or attach a file for lengthier comments. Please go to <https://www.regulations.gov> and follow the on-line instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number. Submitted comments are not instantaneously available for public view on *Regulations.gov*. If you have received a Comment Tracking Number, you have submitted your comment successfully and there is no need to resubmit the same comment. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 PM Eastern Time on the last day of the comment period.

- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary and are discouraged. Should you wish to mail a paper comment *in lieu of* an electronic format, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrisette Drive, Springfield, Virginia 22152.

- *Hearing requests:* All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law asserted in the hearing, must be sent to: Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrisette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug & Chemical

Evaluation Section, Diversion Control Division, Drug Enforcement Administration;

Telephone: (571) 362-3249.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

All comments received in response to this docket are considered part of the public record. The Drug Enforcement Administration (DEA) will make comments available, unless reasonable cause is given, for public inspection online at <https://www.regulations.gov>. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want DEA to make it publicly available, you must include the phrase “PERSONAL IDENTIFYING INFORMATION” in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want DEA to make it publicly available, you must include the phrase “CONFIDENTIAL BUSINESS INFORMATION” in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

DEA will generally make available in publicly redacted form comments containing personal identifying information and confidential business information identified, as directed above. If a comment has so much confidential business information or personal identifying information that DEA cannot effectively redact it, DEA may not make all or part of that comment publicly available. Comments posted to

<https://www.regulations.gov> may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as confidential as directed above.

An electronic copy of this document and supplemental information to this proposed rule are available at <https://www.regulations.gov> for easy reference.

Request for Hearing or Appearance; Waiver

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking “on the record after opportunity for a hearing.” Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (5 U.S.C. 551–559). 21 CFR 1308.41–1308.45, and 21 CFR part 1316, subpart D. Interested persons may file requests for a hearing or notices of intent to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(a) or (b), and such requests must include a statement of the interest of the person in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. 21 CFR 1316.47(a). Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person’s position on the matters of fact and law involved in any hearing as set forth in 21 CFR 1308.44(c).

Please note that, pursuant to 21 U.S.C. 811(a)(2), the purpose of a hearing would be to determine whether fenfluramine should be removed from the list of controlled substances based on a finding that the drug does not meet the requirements for inclusion in any schedule. All requests for hearing and waivers of participation, together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information above.

Legal Authority

The Controlled Substances Act (CSA) provides that proceedings for the issuance, amendment, or repeal of the scheduling of any drug or other substance may be initiated

by the Attorney General (1) on his own motion, (2) at the request of the Secretary of the Department of Health and Human Services (HHS),¹ or (3) on the petition of any interested party. 21 U.S.C. 811(a). This action was initiated by a petition to remove fenfluramine from the list of scheduled controlled substances of the CSA, and is supported by, *inter alia*, a recommendation from the Assistant Secretary for Health of HHS and an evaluation of all relevant data by DEA. If finalized, this action would remove the regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances, including those specific to schedule IV controlled substances, on persons who handle or propose to handle fenfluramine.

Background

Fenfluramine (chemical name: *N*-ethyl- α -methyl-3-(trifluoromethyl)phenethylamine), including its salts, isomers, and salts of such isomers, is currently controlled under 21 CFR 1308.14(d) as a schedule IV substance of the CSA. DEA placed fenfluramine in schedule IV on June 15, 1973 (38 FR 15719), after the U.S. Food and Drug Administration's (FDA) approval on June 14, 1973 of Pondimin, a fenfluramine product manufactured by Wyeth Pharmaceuticals, for the management of exogenous obesity. As noted in the HHS review of scientific and medical information, on September 25, 2019, Zogenix, Inc. (Zogenix; the Sponsor) submitted to FDA a New Drug Application (NDA) for Fintepla (fenfluramine),² for the treatment of seizures associated with Dravet syndrome (DS) in patients two years of age and older. (HHS, 2021) FDA approved the NDA on June 25, 2020, with the labelling listing fenfluramine as a schedule IV controlled substance.

¹The Secretary of HHS has delegated to the Assistant Secretary for Health the authority to make domestic drug scheduling recommendations.

² Fintepla is an oral solution that contains 2.2 mg/ml fenfluramine equivalent to 2.5 mg/ml of the hydrochloride salt.

On March 18, 1991, Interneuron Pharmaceuticals, Inc., the manufacturer of a fenfluramine product (dexfenfluramine, brand name Redux), petitioned DEA to decontrol fenfluramine. In response to DEA's request, HHS's Assistant Secretary for Health submitted to DEA a scientific and medical evaluation (HHS review) and a scheduling recommendation to DEA to decontrol fenfluramine on June 3, 1996. On May 6, 1997, DEA published a notice of proposed rulemaking (NPRM) in the *Federal Register* to remove fenfluramine from controls under the CSA. 62 FR 24620. On July 8, 1997, FDA issued a public health advisory regarding the use of fenfluramine, especially in conjunction with phentermine (schedule IV controlled substance) commonly known as "phen-fen," citing evidence of significant side effects associated with fenfluramine. FDA announced a voluntary withdrawal by the pharmaceutical manufacturers of Pondimin (fenfluramine) and Redux (dexfenfluramine) from the U.S. market on September 15, 1997. HHS issued a final rule on March 8, 1999, listing drug products that were withdrawn or removed from the market because they were found to be unsafe or not effective, including fenfluramine hydrochloride. 64 FR 10944. On February 27, 2003, Indevus Pharmaceuticals, Inc., formerly known as Interneuron Pharmaceuticals, Inc., wrote to DEA to withdraw its petition to decontrol fenfluramine because it no longer markets fenfluramine products in the U.S. In light of the above-mentioned developments, on May 15, 2003, DEA withdrew the May 1997 NPRM. 68 FR 26247.

On October 18, 2018, Zogenix submitted to DEA a petition requesting that fenfluramine be removed from schedule IV of the CSA based on the data and rationale in DEA's May 1997 NPRM and more recent data collected, including data specific to Fintepla. The petition complied with the requirements of 21 CFR 1308.43(b) and DEA accepted the petition for filing on November 13, 2018.

Proposed Determination to Decontrol Fenfluramine

Pursuant to 21 U.S.C. 811(b), on September 22, 2020, DEA, having gathered the necessary data on fenfluramine, forwarded that data and the petition to HHS with a request for scientific and medical evaluation and scheduling recommendation for fenfluramine. On April 16, 2021, DEA received from HHS a scientific and medical evaluation conducted by FDA entitled “Basis for the recommendation to remove fenfluramine (*N*-ethyl- α -methyl-3-(trifluoromethyl)phenethylamine) and its salts from all schedules of control under the Controlled Substances Act” and a scheduling recommendation. The National Institute on Drug Abuse (NIDA) concurred with the scientific and medical evaluation conducted by FDA. Based on the totality of the available scientific data, fenfluramine does not conform with the findings for schedule IV in 21 U.S.C. 812(b)(4) or in any other schedule as set forth in 21 U.S.C. 812(b). Based on FDA’s scientific and medical review of the eight factors and findings related to the substance’s abuse potential, legitimate medical use, and dependence liability, HHS recommended that fenfluramine and its salts be removed from all schedules of the CSA.

The CSA requires DEA, as delegated by the Attorney General,³ to determine whether HHS’s scientific and medical evaluation, scheduling recommendation, as well as all other relevant data constitute substantial evidence that a substance should be scheduled. 21 U.S.C. 811(b). DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, and all other relevant data, and completed its own eight-factor review document on fenfluramine pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in this proposal to remove fenfluramine from the schedules of the CSA. Both DEA and HHS analyses are available in their entirety under “Supporting and Related Material” of the public docket for this rule at <https://www.regulations.gov> under docket number DEA-945.

³ 28 CFR 0.100(b).

1. The Drug's Actual or Relative Potential for Abuse.

The first factor DEA must consider is the actual or relative potential for abuse of fenfluramine. The term “abuse” is not defined in the CSA. However, the legislative history of the CSA suggests the following points in determining whether a particular drug or substance has a potential for abuse:⁴

a. Whether there is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

As HHS noted, FDA approved fenfluramine (brand name Pondimin) in the U.S. on June 14, 1973, but FDA announced on September 15, 1997 that the pharmaceutical manufacturers of Pondimin and Redux (another FDA-approved fenfluramine product) voluntarily withdrew their products from the U.S. markets (see 68 FR 26247; May 15, 2003) after FDA issued a public health advisory in May 1997. FDA’s public health advisory reported increased rates of cardiac valvulopathy and pulmonary arterial hypertension (PAH) related to fenfluramine use, particularly when used in the unapproved combination with phentermine for weight loss. On June 25, 2020, FDA approved Fintepla for the treatment of seizures associated with DS in patients two years of age and older. HHS noted in their scientific and medical evaluation that FDA reviewed the known hazards of fenfluramine and found no evidence of cardiac valvulopathy or PAH in pediatric DS patients treated with fenfluramine in the cardiovascular data the Petitioner submitted as part of their NDA application. FDA concluded that there is a reduced risk of cardiac valvulopathy or PAH due to the lower doses used to treat pediatric DS patients relative to the higher doses prescribed to obese adult patients. DEA notes that the FDA-approved labeling for Fintepla indicates that

⁴ Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970); 1970 U.S.C.C.A.N. 4566, 4603.

patients must be enrolled in the Fintepla risk evaluation and mitigation strategy (REMS) program and undergo cardiac monitoring before, during, and after treatment with fenfluramine to monitor for serious heart valve changes or high blood pressure in the arteries of the lungs.

b. Whether there is significant diversion of the drug or drugs containing such a substance from legitimate drug channels.

Fenfluramine was previously marketed in the U.S. from 1973 to 1997. According to DEA's forensic laboratory database System to Retrieve Information from Drug Evidence (STRIDE),⁵ 30 cases of fenfluramine were recorded between 1973 to 1991. Seven reports occurred in 1988 and involved seizures of fenfluramine from individuals traveling from Mexico into the U.S. Twenty-three drug seizure reports occurred after the manufacturers' voluntary withdrawal, in September 1997, of Pondimin and Redux from the U.S. market (1999 to 2009) in seven states and the District of Columbia. According to DEA's National Forensic Laboratory Information System-Drug (NFLIS-Drug),⁶ 177 seizures were reported from January 1997 to November 2021 in 30 states and the District of Columbia, with eight of the encounters reported from January 2017 through November 2021. In 169 of the encounters reported, fenfluramine was reported alone, with another encountered with only cellulose noted, a common filler or cutting agent. Fenfluramine was commonly encountered as a powder, capsule, or tablet.

⁵ STRIDE reflects the results of drug evidence analyzed at DEA laboratories through September, 2014. STRIDE was queried on July, 3, 2019.

⁶ NFLIS-Drug is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by local, State, and Federal forensic laboratories in the United States. NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle more than 96% of an estimated 1.0 million distinct annual State and local drug analysis cases. While NFLIS-Drug data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332, Dec. 12, 2011. NFLIS-Drug was queried on December, 20, 2021. Some 2021 reports to NFLIS-Drug may still be pending.

Additionally, DEA's May 1997 NPRM included data on fenfluramine from the Drug Abuse Warning Network (DAWN).⁷ (62 FR 24620, 24621) The DAWN data showed very little abuse, trafficking, and diversion of fenfluramine. In addition, HHS stated that there were no reports of diversion in clinical trials conducted by the current Petitioner.

c. Whether individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice.

The available evidence suggests that the prevalence of individuals taking fenfluramine on their own initiative, without advice from a licensed medical practitioner, does not occur to a meaningful degree.

d. Whether the drug or drugs containing such a substance are new drugs so related in their action to a substance already listed as having a potential for abuse to make it likely that it will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that they have a substantial capability of creating hazards to the health of the user or to the safety of the community.

According to HHS, fenfluramine is a serotonin (5-HT) releasing agent. Some drugs with the same mechanism of action are controlled in the CSA (e.g., 3,4-methylenedioxymethamphetamine or MDMA (also known as ecstasy, schedule I substance) and some are not. HHS further noted that in animal drug discrimination studies, which are generally sensitive to mechanisms of action, fenfluramine fully

⁷ DAWN is a public health surveillance system that monitors drug-related visits to hospital emergency departments. DAWN was discontinued in 2011, but the Substance Abuse and Mental Health Services Administration's website currently indicates that it is re-establishing this system.

generalized to the discriminative stimulus effects of serotonergic substances such as MDMA, quipazine, and MK-212. The latter two are not controlled substances.

2. Scientific Evidence of the Drug's Pharmacological Effects, If Known.

The binding and activity studies indicate that fenfluramine causes the release and prevents the reuptake of 5-HT; has antagonist activity at the beta-2 adrenergic receptor, the muscarinic M1 receptor, and the sodium ion channel (hNav1.5); and has positive allosteric modulator activity at the nonspecific sigma-1 receptor.

Additionally, *d*-fenfluramine is a potent agonist of the 5-HT_{2B} receptor despite its weak binding affinity, has moderate agonist activity at the 5-HT_{2C} receptor, and has weak activity at the 5-HT_{2A} receptor, whereas *l*-norfenfluramine demonstrated moderate activity at the 5-HT_{2B} receptor and weak activity at the 5-HT_{2C} and 5-HT_{2A} receptors, respectively.

Drug discrimination assays in animals can be used to predict if a test drug will have abuse potential in humans. Although fenfluramine was first thought of as a stimulant based on its phenethylamine structure, fenfluramine does not generalize to stimulants when the discriminative stimulus effects were tested against a range of stimulant drugs. When rats were trained to discriminate fenfluramine from vehicle or other drugs, it became evident that fenfluramine produced discriminative stimulus effects similar to those of serotonergic substances such as quipazine and MK-212. HHS noted that fenfluramine fully generalized to drugs that do not have abuse potential such as lisuride, quipazine, and 1-(*m*-trifluoro-methylphenyl)piperazine (TFMPP), and generalized to some drugs that have abuse potential such as MDMA, but not to *para*-methoxyamphetamine (PMA, schedule I substance) or LSD (schedule I substance), which generalized to norfenfluramine. HHS concluded the drug discrimination studies are equivocal and do not provide clear evidence of the hallucinogenic effects of fenfluramine, a finding consistent with its clinical effects.

The reinforcing effects of fenfluramine, using various models and animal species, were also reviewed. HHS determined that the fenfluramine responded similarly to placebo and does not produce reinforcing effects. Further, HHS stated that these data are consistent with 5-HT agonists that are phenethylamines and lack stimulant activity. Fenfluramine is a phenethylamine that produces serotonergic agonist activity. Therefore, fenfluramine may be expected to produce placebo-like responding in these reinforcing assays.

According to HHS, after review of the published literature on the subjective effects of fenfluramine in humans, data indicate that single oral doses below 80 mg do not produce significant positive subjective effects. High doses ranging from 120 to 240 mg can produce positive subjective effects; however, the predominant effects at high doses were aversive and included sedation. Anecdotal reports of abuse of fenfluramine from doctors exist; however, the published articles mention the subjects prefer other drugs. HHS mentioned that these effects are consistent with other measures indicating that subjects are tired, do not appreciate the psychoactive effects of fenfluramine, and do not “Want More” of the drug when asked.

HHS noted that Fintepla did not produce a concerning number of abuse-related adverse effects (AEs) after an analysis of the adverse effect profiles of all phases of development was completed. FDA reviewed the cardiovascular data submitted in the NDA for Fintepla and found no evidence of cardiac valvulopathy or PAH in pediatric DS patients treated with fenfluramine. The studies conducted for the NDA for Fintepla concluded that there was a reduced risk of cardiac valvulopathy or PAH because of the lower doses used to treat pediatric DS patients compared to the higher doses prescribed to obese adult patients.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance.

According to HHS, fenfluramine, also known by the developmental code ZX008,

is the nonproprietary name of N-ethyl- α -methyl-3-(trifluoromethyl)phenethylamine hydrochloride and is structurally similar to the amphetamine class of stimulants.

Fenfluramine has one asymmetric carbon and therefore may exist in two forms, which are identified as the (*d*) and the (*l*) enantiomers. Fenfluramine represents a mixture of both enantiomers. The molecular formula of fenfluramine hydrochloride (salt) is $C_{12}H_{16}F_3N \text{ HCl}$ and the molecular weight is 267.72 g/mol. Fenfluramine is a white to off-white powder. Fenfluramine hydrochloride (salt) is soluble in organic solvents like ethanol (150 mg/mL) at 25 °C and dichloromethane (30-35 mg/mL) at 25 °C.

According to HHS, the development of fenfluramine (Fintepla) included a study that assessed the permeability of fenfluramine and norfenfluramine across Caco-2 cells that express P-glycoprotein (P-gp) transporters. P-gp transporters are known to actively transport foreign substances out of cells and the central nervous system (CNS) and can help determine a drug's permeability into the CNS. Both fenfluramine and norfenfluramine are highly permeable and the permeability was not affected by the P-gp antagonist valspodar (10 μM), suggesting fenfluramine and norfenfluramine will pass easily into the CNS.

Pharmacokinetic data indicate that a single oral dose of fenfluramine (20 mg/kg, PO) in mice produced a C_{max} of 0.26 $\mu\text{g/mL}$ and an area under the curve (AUC) of 1.4 $\mu\text{g/mL}\cdot\text{hr}$, results similar to that of a 60 mg twice daily (BID) dose in healthy human adults. The same dose (20 mg/kg, PO) in rats produced a C_{max} of 0.36 $\mu\text{g/mL}$ and an AUC of 5.15 $\mu\text{g/mL}\cdot\text{hr}$, values higher than those in the mouse studies. The T_{max} of fenfluramine in rats ranged from 30 minutes to 2 hours, and the half-life was 2.5 hours.

According to HHS, the Sponsor of the Fintepla NDA provided pharmacokinetic data on norfenfluramine. In rats, a single oral dose of norfenfluramine is rapidly absorbed similarly to fenfluramine, with a T_{max} of 30 minutes and a half-life of 2.5 hours. Fenfluramine and norfenfluramine are easily distributed throughout the body and

produced approximately 50 percent protein specific binding in human and rat plasma, however concentrations of both compounds were determined to be higher in the brain compared to the plasma, by 15 to 60-fold, depending on the study.

Fenfluramine is metabolized to norfenfluramine and is an active metabolite. Norfenfluramine and its *N*-oxygenation product were the only metabolites detected in liver S9 fractions in both rat and human samples. Fenfluramine and norfenfluramine are excreted primarily through the renal system (greater than 80%), with a small amount via the feces.

4. Its History and Current Pattern of Abuse.

HHS noted that sporadic anecdotal reports of fenfluramine abuse were found when fenfluramine was marketed in the United States and Europe between 1963 and 1997. However, when compared to the large number of patients who were treated with and prescribed the drug during this time frame (approximately 55 million patients total, 50 million European patients with fenfluramine, and 5 million U.S. patients with fenfluramine or desfenfluramine), the number of people abusing fenfluramine is relatively small. According to these reports, HHS noted that these individuals either did not like fenfluramine because of its dysphoric effects or preferred another drug. Therefore, the history and current pattern of abuse of fenfluramine is low.

5. The Scope, Duration, and Significance of Abuse.

HHS stated that the scope of abuse of fenfluramine was minimal when it was marketed and when compared to the number of patients to whom it was prescribed. According to HHS, fenfluramine, in most cases, was not the drug of choice to produce a psychoactive effect and was used only when no other drug was available. In most cases, a high dose fenfluramine⁸ produced a dysphoric effect leading the individual to stop

⁸ The HHS review indicated that in human clinical studies and case reports, a single oral dose of 80 mg did not produce significant positive subjective effects; however, high single oral doses of 120 or 240 mg can produce positive subjective effects. Single oral doses over 80 mg were reported to be aversive and produce dysphoric effects.

taking fenfluramine.

DEA conducted a search of Federal, State, and local forensic laboratory databases such as NFLIS-Drug and STRIDE. The STRIDE database indicated that in the 18 years between 1973 and 1991, 30 cases of fenfluramine were entered into the database, and, there were 23 drug seizure reports during the period of 1999 to 2009 in seven states and the District of Columbia. According to NFLIS-Drug, there were 177 reports of fenfluramine from 30 states and the District of Columbia between January 1997 and November 2021. Eight of the 177 encounters were reported from January 2017 through November 2021 (1 in 2017, 3 in 2019, 3 in 2020, 1 in 2021). In 169 of these encounters, fenfluramine was reported alone. Another encounter was with only cellulose, a common filler or cutting agent. Fenfluramine was commonly encountered as a powder, capsule, or tablet.

HHS noted, as a result, the scope, duration, and significance of abuse of fenfluramine are minimal compared to the millions of patients who were prescribed and treated with the drug.

6. What, If Any, Risk There is to the Public Health.

Abuse potential of a drug is considered one indication of its risk to the public health. According to HHS, based on preclinical and clinical study data (see Factors 1 and 2), there are no signals that indicate that fenfluramine has abuse potential or that there is a risk to the public health from individuals abusing fenfluramine.

An FDA public health advisory, released on July 8, 1997, indicated increased rates of cardiac valvulopathy and PAH in relation to the use of fenfluramine, particularly in combination with phentermine. FDA approved Fintepla (fenfluramine) with a boxed warning on the label to address the potential cardiac issues that have been correlated to

the administration of fenfluramine and included language that patients would need to undergo cardiac assessments before, during, and after treatment with the drug.⁹

Thus, HHS concluded there is likely to be little risk to the public health from fenfluramine.

7. Its Psychic or Physiological Dependence Liability.

The psychic dependence of fenfluramine was assessed in animal and clinical studies. HHS reported that fenfluramine failed to produce reinforcing effects in self-administration studies (Factor 2) and indicated that fenfluramine does not produce psychic dependence. HHS also noted there was a lack of psychic dependence in the clinical data discussed in Factors 2 and 4. These data indicate that fenfluramine produces dysphoric effects and that it is not the drug of choice among individuals with a drug use disorder. According to HHS, these data suggest that fenfluramine has low psychic dependence.

As per the physical dependence potential, there are reports of withdrawal syndrome upon cessation of fenfluramine use. HHS noted that a search of the FDA Adverse Event Reporting System (commonly known as FAERS) covering the years fenfluramine was marketed (1973 to 1997) produced four cases of “withdrawal syndrome” associated with fenfluramine. Physical dependence was not assessed in humans throughout the clinical development of fenfluramine (Fintepla). The Phase 1 studies were single dose studies or studies in which treatment was administered for only six days and not long enough to produce dependence. Additionally, physical dependence could not be assessed in the Phase 3 studies because the discontinuation of fenfluramine in seizure patients could not be done abruptly. The Phase 3 studies included a taper phase. The FDA-approved label recommends that fenfluramine be withdrawn gradually.

⁹ DEA notes that this boxed warning also states that Fintepla is available only through a restricted program, Fintepla REMS.
<https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=400>.

In conclusion, HHS noted that the psychic and physiologic dependence potential of fenfluramine is minimal in relation to the number of patients who have been treated with the drug. As a result, HHS stated that the number of reports of psychic and physiologic dependence potential of fenfluramine is low.

8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled Under the CSA.

Fenfluramine is not an immediate precursor of a substance already controlled under the CSA as defined by 21 U.S.C. 802(23).

Conclusion:

Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and based on DEA's consideration of its own eight-factor analysis, the Administrator of DEA (Administrator), pursuant to 21 U.S.C. 811(a) and (c), finds that these facts and all relevant data demonstrate that fenfluramine does not meet the requirements under 21 U.S.C. 812(b) for inclusion in any schedule, and should be removed from control under the CSA. Specifically, the Administrator finds the following:

(1) Fenfluramine appears to have no potential for abuse. According to HHS, the profile of activity for fenfluramine differs from other 5-HT agonists that are phenethylamines as it does not generalize to a stimulant. In addition, the *in vitro*, animal, human, and epidemiology data indicate that fenfluramine has no potential for abuse.

(2) Fenfluramine has a currently accepted medical use in treatment in the United States. FDA approved the NDA for Fintepla (fenfluramine) on June 25, 2020 for the treatment of DS in patients aged two years and older.

(3) Fenfluramine does not appear to have psychological or physical dependence liability. According to HHS, the reports of psychic or physiologic dependence of fenfluramine are minimal when viewed in the context of large number of patients who were treated with

the drug in the United States and Europe between 1963 and 1997. Thus, the psychic and physiological dependence liability of fenfluramine is lower than that of substances in schedules IV and V.

Based on these findings, the Administrator concludes that fenfluramine does not meet the requirements for inclusion in any schedule and should be removed from control under the CSA.

Regulatory Analyses

Executive Orders 12866 (Regulatory Planning and Review) and 13563 (Improving Regulation and Regulatory Review)

In accordance with 21 U.S.C. 811(a), this proposed scheduling action is subject to formal rulemaking procedures done “on the record after opportunity for a hearing,” which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the criteria for removing a drug or other substance from the list of controlled substances. Such actions are exempt from review by the Office of Management and Budget pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

Executive Order 12988, Civil Justice Reform

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This proposed rulemaking does not have federalism implications warranting the application of E.O. 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the National Government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination with Indian Tribal Governments

This proposed rule does not have tribal implications warranting the application of E.O. 13175. This proposed rule does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612), has reviewed this proposed rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. The purpose of this rule is to remove fenfluramine from the list of schedules of the CSA. This action will remove regulatory controls and administrative, civil, and criminal sanctions applicable to controlled substances for handlers and proposed handlers of fenfluramine. Accordingly, it has the potential for some economic impact in the form of cost savings.

If finalized, the proposed rule will affect all persons who would handle, or propose to handle fenfluramine. Fenfluramine as a pharmaceutical product (Fintepla) is currently available and marketed in the U.S. Because fenfluramine is currently a schedule IV drug, all legal handling of fenfluramine is currently done under appropriate DEA license. In such instances, DEA's knowledge of its registrant population forms the basis for estimating the number of affected entities and small entities that are affected by this rulemaking. There are currently 40 unique registrations authorized to handle fenfluramine specifically, as well as a number of registered analytical labs that are authorized to handle schedule IV controlled substances generally. From review of entity names, DEA estimates these 40 registrations represent 27 entities. Some of these entities are likely to be small entities. However, since DEA does not have information of registrant size and the majority of DEA registrants are small entities or are employed by

small entities, DEA estimates a maximum of 27 entities are small entities. Therefore, DEA conservatively estimates as many as 27 small entities are affected by this proposed rule. However, because this rule would remove fenfluramine from regulatory controls of the CSA, it is likely to result in some cost savings. Any person planning to handle fenfluramine will realize cost savings in the form of saved DEA registration fees, and the elimination of physical security, recordkeeping, and reporting requirements. Because of these factors, DEA projects that this rule will not result in a significant economic impact on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

On the basis of information contained in the “Regulatory Flexibility Act” section above, DEA has determined pursuant to the Unfunded Mandates Reform Act (UMRA) of 1995, (2 U.S.C. 1501 *et seq.*), that this proposed action would not result in any Federal mandate that may result “in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any 1 year. . . .” Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Paperwork Reduction Act of 1995

This proposed action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995. (44 U.S.C. 3501–3521).

Signing Authority

This document of the Drug Enforcement Administration was signed on July 13, 2022, by Administrator Anne Milgram. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer has been authorized to sign and submit the document in electronic format

for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the Federal Register.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA proposes to amend 21 CFR part 1308 as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

1. The authority citation for 21 CFR part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

§ 1308.14 [Amended]

2. In § 1308.14, remove and reserve paragraph (d).

Scott Brinks,
Federal Register Liaison Officer,
Drug Enforcement Administration.